Remarks

Reconsideration of this Application is respectfully requested. Upon entry of the foregoing amendment, claims 1-21 are pending in the application, with 1, 5, 8 and 15 being the independent claims. Claims 22-54 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claim 5 has been amended to incorporate the subject matter of claim 1, from which it previously depended. Claim 5 has also been amended to include a translocating domain of clostridial neurotoxin, which finds support in the specification, for example, at page 7, paragraph 0024. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Obviousness Type Double Patenting Rejection

Claims 1-4, 6-11, 13-18, 20 and 21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 9 and 14 of U.S. Patent 6,632,440. Office Action, page 3, paragraph 2. Applicants respectfully traverse the rejection. However, solely to expedite prosecution and not in acquiescence to the rejection, Applicants provide herewith a terminal disclaimer over U.S. Patent No. 6,632,440, signed by an attorney of record. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejections Under 35 U.S.C. § 112

Claims 1-4, 6-11, 13-18, 20 and 21 are rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly

> . . . does not reasonably provide enablement for a method of treating hypersecretion of mucus, asthma and COPD, administering topically to the airways of a patient in need thereof, a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin containing the active proteolytic enzyme domain, a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, and a translocating domain that translocates the L-chain or L-chain fragment into the target cell, with the proviso that the compound is not a botulinum toxin, *wherein the translocating domain is not identified.*

Office Action, page 5, paragraph 3 (emphasis added). The Examiner has alleged that the only methods that are enabled by the specification are those that use a compound having a translocating domain of a clostridial neurotoxin, or as defined in the table on page 8 of Applicants' specification, with the proviso that the compound is not a botulinum toxin. *Id.* Applicants respectfully traverse this rejection.

The M.P.E.P. provides guidance to examiners with respect to when enablement is commensurate in scope with the claims. In particular, the M.P.E.P. states that

> [t]he Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331,1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

M.P.E.P. 8th ed., § 2164.08 (Rev. 2, May 2004).

Applicants' claims are enabled because their scope is commensurate with what is enabled by the specification in light of that which is well known by the skilled artisan. The claims are directed to methods of treating hypersecretion of mucus, chronic obstructive pulmonary disease or asthma using a compound having three components. The third component, a translocating domain, is both limited by the claim language and readily recognized by the skilled artisan. The claims recite that the translocating domain have the property of translocating the L-chain or L-chain fragment into the target cell. Moreover, this claim language is fully explained and exemplified in Applicants' specification such that the skilled artisan would know how to make and use the full scope of the compounds according to the claimed methods without undue experimentation.

Translocating domains suitable for use in the agents of the present invention have a common function in that they deliver the L-chain or L-chain fragment into the cell by a process of endocytosis. See Applicants' specification, page 9, paragraph 0030. In this regard, the only functional requirement of a translocation domain of the present invention is that it is capable of releasing the L-chain or L-chain fragment from the endosome. Such release is widely recognized by the skilled artisan and is termed "endocytic release".

As detailed in the present specification, suitable translocation domains can be obtained from a wide range of sources. Applicants' specification indicates, for example, that such domains can be obtained from microbial sources such as bacterial or viral sources. See Applicants' specification, page 7, paragraphs 0023 to 0025. A translocating domain can be an enzyme, such as a bacterial or viral toxin, which includes the

translocating domain of clostridial neurotoxin or diphtheria toxin, or domain II of pseudomonas exotoxin.

Alternatively, as described in the present specification, the translocating activity of the presently claimed agents can be derived from a virally expressed membrane fusion protein. Examples of such suitable proteins include influenza virus haemagglutinin, semliki forest virus fusogenic protein, vesicular stomatitis virus glycoprotein G, SER virus F protein and foamy virus envelope glycoprotein. See Applicants' specification, page 7, paragraph 0025. Virally encoded "spike proteins" such as the E1 protein of SFV and the G protein of VSV can also provide the requisite translocating activity. *Id.*

Furthermore, a skilled person reading the present specification would be able to identify suitable translocating domains for use in the present invention as a routine matter. By way of example, suitable methodologies are described in Applicants' specification at pages 7-9, paragraphs 0027 to 0030. These paragraphs refer to Shone, C. C. *et al., Eur. J. Biochem. 167:* 175-180 (1987) and Blaustein, R. O. *et al., FEBS Letters 226*: 115-120 (1987), which were previously cited as documents AT5 and AR4 (respectively) in Applicants' First Supplemental Information Disclosure Statement, filed Augst 5, 2003. These documents are provided herewith for the Examiner's convenience as Exhibits A and B. Shone *et al.* and Blaustein *et al.* demonstrate that the skilled artisan can routinely identify translocation domains for compounds useful according to the claimed methods without undue experimentation.

As provided herewith as Exhibit C, Lord, J. M. *et al., Cellular Microbiology 1*: 85-91 (1999) provides an overview of internalisation pathways that are routed via the early endosome. In particular, the "H+" internalisation pathway (exemplified by

clostridial neurotoxin) and "ER" internalisation pathway (exemplified by PE, shiga toxin and ricin). Whilst these pathways are distinct and have many differences, they share a common route (i.e. via the endosome) for translocation of active material into the cytosol. This common route of transportation is well known to those skilled in the art, as are molecules that are internalised by this pathway. Moreover, a skilled person would consider it routine to identify such molecules.

Further examples of molecules that have the desired translocating activity include anthrax PA83 and the C. *botulinum* C_2 domain. As described in Zhang, S. *et al.*, *Biophys. J. 87*: 3842-9 (2004) (abstract provided herewith as Exhibit D), anthrax PA63 forms a heptameric channel in the endosome membrane in order to translocate the active components (LF or EF) into the cytosol. Haug, G. *et al., Biochem. 42*: 15284-91 (2003) (abstract provided herewith as Exhibit E) reports that heptameric pores are also used by the *C. botulinum* C_2 domain (C2II domain) for translocation of the active domain across the endosomal membrane.

Applicants note that the present invention does not embrace simple membrane permeable peptides, such as those described in Sandvig, K. *et al.*, *Int. J. Med. Microbiol. 293*: 483-90 (2004) (abstract provided herewith as Exhibit F), which transport directly into the cytosol from the extracellular milieu. This "direct delivery" pathway is entirely different from the pathway used by the translocating domains of the present invention, which go through the endosomal release pathway.

In conclusion, Applicants' method claims are directed to use of a compound comprising (among other elements) a translocating domain that translocates the L-chain

or L-chain fragment into the target cell. Applicants claims are enabled across the full scope of "translocating domain" for the following reasons:

- the claim requires the "translocating domain" to have the property of being capable of translocating the L-chain or L-chain fragment into the target cell;
- a wide range of translocating domains having similar biological function and properties are described and exemplified in Applicants' specification;
- Applicants' specification describes how the skilled artisan would recognize translocating domains capable of being used without undue experimentation in the compounds of the claimed methods;
- Applicants' specification describes publications demonstrating that the skilled artisan can routinely identify translocating domains capable of being used without undue experimentation in the compounds of the claimed methods;
- Applicants have provided additional publications evidencing the fact that the skilled artisan would regard the identification of translocating domains to be routine.

Hence, the skilled artisan upon reading Applicants' disclosure would know how to make and use the compounds useful according to the claimed methods without undue experimentation. Thus, Applicants' method claims are fully enabled by their specification. Accordingly, Applicants request that the Examiner reconsider and withdraw this rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Aaron L. Schwartz
Attorney for Applicants
Registration No. 48,181

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
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